

**Translation**

**PATENT COOPERATION TREATY**

**PCT**

**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY**

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>30073P WO</b>	<b>FOR FURTHER ACTION</b>	See Form PCT/IPEA/416
International application No. <b>PCT/EP2004/002850</b>	International filing date (day/month/year) <b>18.03.2004</b>	Priority date (day/month/year) <b>19.03.2003</b>
International Patent Classification (IPC) or national classification and IPC		
Applicant <b>KTB TUMORFORSCHUNGS GMBH</b>		

1.	This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.	
2.	This REPORT consists of a total of <u>8</u> sheets, including this cover sheet.	
3.	This report is also accompanied by ANNEXES, comprising: a. <input type="checkbox"/> (sent to the applicant and to the International Bureau) a total of _____ sheets, as follows: <input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). <input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).	
4.	This report contains indications relating to the following items: <input checked="" type="checkbox"/> Box No. I Basis of the report <input type="checkbox"/> Box No. II Priority <input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability <input type="checkbox"/> Box No. IV Lack of unity of invention <input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement <input type="checkbox"/> Box No. VI Certain documents cited <input type="checkbox"/> Box No. VII Certain defects in the international application <input type="checkbox"/> Box No. VIII Certain observations on the international application	

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/EP	Authorized officer
Facsimile No.	Telephone No.

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/EP2004/002850

## Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language \_\_\_\_\_, which is the language of a translation furnished for the purposes of:
- ☐ international search (Rule 12.3 and 23.1(b))
- ☐ publication of the international application (Rule 12.4)
- ☐ international preliminary examination (Rule 55.2 and/or 55.3)
2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:
- ☐ the international application as originally filed/furnished
- ☒ the description:
- pages 1-18 \_\_\_\_\_ as originally filed/furnished
- pages\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_
- pages\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_
- ☒ the claims:
- nos. 1-15 \_\_\_\_\_ as originally filed/furnished
- nos.\* 19-24 \_\_\_\_\_ as amended (together with any statement) under Article 19
- nos.\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_
- nos.\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_
- ☒ the drawings:
- sheets 1/1 \_\_\_\_\_ as originally filed/furnished
- sheets\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_
- sheets\* \_\_\_\_\_ received by this Authority on \_\_\_\_\_
- ☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages \_\_\_\_\_
- ☐ the claims, nos. \_\_\_\_\_
- ☐ the drawings, sheets/figs \_\_\_\_\_
- ☐ the sequence listing (*specify*): \_\_\_\_\_
- ☐ any table(s) related to sequence listing (*specify*): \_\_\_\_\_
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages \_\_\_\_\_
- ☐ the claims, nos. \_\_\_\_\_
- ☐ the drawings, sheets/figs \_\_\_\_\_
- ☐ the sequence listing (*specify*): \_\_\_\_\_
- ☐ any table(s) related to sequence listing (*specify*): \_\_\_\_\_

\* If item 4 applies, some or all of those sheets may be marked "superseded."

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

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## Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 14

because:

☒ the said international application, or the said claims Nos. \_\_\_\_\_  
relate to the following subject matter which does not require an international preliminary examination (*specify*):

Claim 14 relates to subject matter which, in the  
opinion of this Authority, falls under PCT  
Rule 67.1(iv). Consequently, no expert opinion has  
been established in respect of the industrial  
applicability of the subject matter of said claims  
(PCT Article 34(4)(a)(i)).

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. \_\_\_\_\_  
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. \_\_\_\_\_ are so inadequately supported  
by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. \_\_\_\_\_

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative  
Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the  
technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/EP2004/002850

Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement		
1. Statement			
Novelty (N)	Claims	1-15	YES
	Claims		NO
Inventive step (IS)	Claims	1-15	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-13, 15	YES
	Claims		NO
2. Citations and explanations (Rule 70.7)			
Reference is made to the following documents:			
D1: PASHKOVSKII F.S., KHLEBNIKOVA T.S., LAKHVICH F.A.: "GENERAL APPROACH TO SYNTHESIS OF CARBOPLATIN ANALOGUE CONTAINING FRAGMENTS OF CARBOXYLIC FATTY ACIDS IN ACID LIGAND", BELARUSKAYA NAVUKA, vol. 46, no. 4, 2002, pages 63-65, XP009033021			
D2: US-A-5 011 959 (KHOKHAR ABDUL R) 30 April 1991 (1991-04-30)			
D3: BOECKLER C ET AL: "Immunogenicity of new heterobifunctional cross-linking reagents used in the conjugation of synthetic peptides to liposomes", JOURNAL OF IMMUNOLOGICAL METHODS, ELSEVIER SCIENCE PUBLISHERS B.V, AMSTERDAM, NL, vol. 191, no. 1, 10 May 1996 (1996-05-10), pages 1-10 XP004020848 ISSN: 0022-1759			
D4: LEBWOHL D ET AL: "Clinical development of platinum complexes in cancer therapy: an historical perspective and an update", EUROPEAN JOURNAL OF CANCER, PERGAMON PRESS, OXFORD, GB, vol. 34, no. 10, September 1998 (1998-09), pages 1522-1534, XP004285042 ISSN: 0959-8049.			

Box No. V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The application relates to low molecular weight platinum complexes of cyclobutan-1,1-dicarboxylate ligands, which contain a protein-binding group, and to the production and use thereof.

**1. PCT Article 33(2)**

The aforementioned documents D1, D2 and D4, cited in the search report, relate to carboplatin analogues. However, only D1 discloses a linker bound to the cyclobutane substructure.

Although document D1 discloses carboplatin analogues containing fragments of saturated or unsaturated carboxylic acids in the acidic ligand, *inter alia* the cis-diammine[3-(octadeca-9,12-dieneamido)-1,1,-yclobutanedicarboxylato]platinum (II), the subject matter of the present application can be considered novel (PCT Article 33(2)) in view of the absence of the protein-binding group in these complexes.

**2. PCT Article 33(3)**

The technical problem addressed by the application can be considered to be that of identifying further carboplatin derivatives that can be used for treating cancer (see figure 1).

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Box No. V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The solution to the above problem, as proposed in the present application, lies in devising carboplatin derivatives that contain a protein-binding group. As a result, the claimed platinum complexes bind rapidly and covalently to serum proteins via the protein-binding group, a macromolecular transport form of the active ingredient being thereby generated.

The closest prior art is document D1, which also discloses carboplatin analogues, the linker thereof being likewise bound to the cyclobutyl ring. However, this linker is a fatty acid linker that contains neither repetitive ethoxy groups nor a protein-binding group. In consequence, the carboplatin analogues of D1 do not have covalent protein-binding properties.

Polyoxyethylene linkers with a thiol-binding group, which is suitable *per se* for binding to free cystein groups on the surface of proteins, were disclosed in document D3 (published in 1996). However, since these are used for liposomal systems and D3 contains nothing to suggest that they can be attached to platinum compounds, said document cannot be used as evidence against the involvement of an inventive step in the present application.

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Box No. V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;  
citations and explanations supporting such statement

For this reason, the present application is considered to involve an inventive step (PCT Article 33(3)).

**3. (PCT Article 34(4))**

The PCT Contracting States do not have uniform criteria for assessing the industrial applicability of the subjects of claim 14 in its present form. Patentability may also depend on the wording of the claims. The EPO, for example, does not recognise the industrial applicability of claims to the medical use of a compound; it may, however, allow claims to the first medical application of a known compound or to the use of such a compound in the manufacture of a drug for a new medical application.